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| EXAMINER | |
|---|---|
| HINES, JANA A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 03/02/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/509,498 | REIMANN ET AL. | |
| | Examiner | Art Unit | |
| | JaNa Hines | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6 and 8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 21, 2010 has been entered.

### *Claim Amendment*

2. The amendment filed February 5, 2010 has been amended. Claims 1 and 10 have been amended. Claims 1-6 and 8-12 are under consideration in this Office Action.

### *Withdrawal of Rejections*

3. The rejection of claims 1-6 and 8-12 under 35 U.S.C. 102(b) as being anticipated by Dalemans et al., (WO 99/30733) is withdrawn in view of applicants amendments.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-6 and 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dalemans et al., (WO 99/30733 published June 24, 1999) in view of Volkin et al., (WO 00/02591 published January 20, 2000).

Claim 1 is drawn to an immunogenic composition suitable for administration to a vertebrate host which comprises: a composition comprising a protein antigen immunogenic component comprising at least one protein antigen selected from the group consisting of model protein antigens and immunogenic protein antigens and a mineral-based, negatively charged adjuvant; and (b) a polynucleotide immunogenic component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said polynucleotide immunogenic component into said vertebrate host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune, said composition produced by a method comprising preincubating or subsequently mixing said mineral-based negatively charged adjuvant with said at least one protein antigen immunogenic component to form the composition of (a) prior to formulating with said polynucleotide immunogenic component. Claims 2-6 are drawn to the adjuvant and the immunogenic protein antigens. Claim 8 is drawn to the kit comprising the immunogenic composition.

Claim 9 is drawn to a method of making the combined immunogenic composition as defined in claim 1, comprising preincubating or subsequently mixing the mineral-based, negatively charged adjuvant with said at least one protein antigen immunogenic component; and adding said polynucleotide immunogenic component to

the adjuvant protein mixture to form the combined immunogenic composition, wherein the immunogenic composition is capable of inducing a prophylactic or therapeutic Th1 and Th2 immune response.

Claim 10 is drawn to an immunogenic composition suitable for administration to a human host which comprises: (a) a composition comprising a protein antigen immunogenic component comprising at least one protein antigen selected from the group consisting of model protein antigens and immunogenic protein antigens and a mineral-based negatively charged adjuvants; and (b) a polynucleotide immunogenic component comprising at least one polynucleotide encoding at least one antigen, such that introduction of said polynucleotide immunogenic component into said human host results in expression of a biologically effective amount of said antigen or antigens so as to induce a prophylactic or therapeutic immune response wherein said mineral-based negatively charged adjuvant is preincubated or subsequently mixed with said at least one protein antigen immunogenic component to form the composition of (a) prior to formulating with said polynucleotide immunogenic component. Claim 11 is drawn to a kit.

Claim 12 is drawn to method for preparing the immunogenic composition according to claim i, wherein a mineral-based negatively charged adjuvant is preincubated or subsequently mixed with at least one protein antigen immunogenic component prior to formulating with a polynucleotide immunogenic component, wherein the immunogenic composition is capable of inducing a prophylactic or therapeutic Th1 and Th2 immune response.

Dalemans et al., teach administration of combination DNA vaccines to mammals such as man (page 3, lines 28-30). Dalemans et al., teach DNA vaccines by admixing two different compounds wherein the first compound comprises a polynucleotide (nucleic acid) such as DNA or RNA which-encodes a selected polypeptide that can stimulate protective immunity and the second compound comprises a polypeptide, which preferably is the same polypeptide (or substantially the same, i.e., having the same immunodominant epitope(s) encoded by the nucleic acid (page 5-6, lines 29-2). When nucleic acid such as DNA encoding the gene of interest is admixed with the corresponding polypeptide is administered to a mammal, a synergistic effect is observed wherein not only is the DNA vaccine capable of inducing an immune response in the presence of protein (polypeptide), but the presence of such protein (polypeptide) has been found to actually enhance the efficacy of the DNA vaccine (page 6, lines 6-11). Thus, one aspect of the present invention is a composition comprising a polynucleotide and polypeptide for enhancing an immune response wherein the polypeptide is adjuvanted (page 6, lines 11-14). Dalemans et al., teach prior mixing of the polypeptide or protein antigen with the adjuvant.

The polynucleotide comprises DNA or RNA polynucleotide sequences coding for polypeptides that have useful therapeutic application, e.g., prophylactic or therapeutic vaccines (page 7, lines 14-16). The combination of DNA + protein, when administered, exhibits a more balanced Th1 + Th2 response, and act synergistically (page 7, lines 16-17). Both expressible DNA and RNA can-be delivered to cells to form therein a polypeptide translation product wherein the encoded antigens are associated with

infectious diseases caused by, for instance, all forms of Hepatitis and polio (page 5, lines 17-22). The protein antigen can be a polypeptide that also has useful therapeutic application such as a prophylactic or therapeutic vaccine (page 6, lines 20-21). The vaccine composition is not limited to a particular polypeptide and can have the same immunodominant epitopes encoded by the nucleic acid (page 6, lines 21-22). Dalemans et al., teach that the polypeptide or protein antigen component can comprise an antigen a surface protein or an antigen derived from inactivated polio virus. Dalemans et al., teach the administration of a polynucleotide/polypeptide composition, should enhance the induction of immunity because the administration of one compound also both components to act during the same ongoing immune response (page 7, lines 25-29 and page 8, line 10). The polynucleotide + polypeptide mixture (complex), when adjuvanted, is preferably adjuvanted with suitable adjuvants that include an aluminum salt such as aluminum hydroxide (alum), aluminum phosphate, but also can be a salt of calcium (page 18-25). Therefore, Dalemans et al., teach a mineral-based, an aluminum or calcium salt, such as aluminum hydroxide and aluminum phosphate, which is a negatively charged adjuvant.

Dalemans et al., teach a method of using the adjuvant as a component in a combined DNA/protein vaccine composition. Dalemans et al., teach that the vaccine formulation includes an adjuvant that encodes CpG sequences, wherein such CpG sequences, or motifs, are known in the art (page 10, lines 4-6). The art teaches that palindromic CpG sequences have immunostimulatory activities and are instrumental in aiding DNA vaccine by providing an activation signal to antigen presenting cell. The

instant specification at page 5, lines 12-15 define model protein antigens as a protein which is not derived from an infectious microorganism which may cause one or more diseases with the aim of eliciting a protective immune response towards the model protein itself. The CpG sequence meets the limitation of being a model protein antigen since CpG is not derived from an infectious microorganism which may cause one or more diseases and the protein does not elicit a protective immune response towards. CpG. Dalemans et al., teach the inclusion of a model protein. Dalemans et al., teach that the composition is packaged in a per unit dosage, unit dosage ampoules or multidose containers, in which the polynucleotides and polypeptides are packaged prior to use enclosing an amount of polynucleotide and polypeptide or solution containing a polynucleotide and polypeptide suitable for a pharmaceutically effective dosing (page 11, lines 2-30). Dalemans et al., teach a unit dose form for administration to a vertebrate recipient. Dalemans et al., also teach a kit comprising the vaccine composition in unit dosage form and a method of using the adjuvant as a component in the combined DNA/protein vaccine composition.

Volkin et al., teach DNA vaccine formulations wherein the adjuvant comprises mineral-based particles which are negatively charged and the particles possess a sufficient negative charge as to substantially retard binding to the nucleic acid molecule of interest (page 5, lines 2-5). Volkin et al., teach the adjuvanted composition will increase the immune response and decrease nuclease digestion of the DNA within the vertebrate host subsequent to immunization (page 5, lines 5-7). Volkin et al., teach the vaccine formulation having aluminum phosphate based adjuvants (page 5, lines 12-13).

Adjuvants have been historically used to enhance the immune response safely in humans, including calcium phosphate, aluminum phosphate, aluminum hydroxyphosphate, and aluminum hydroxide (page 3, lines 6-14). Volkin et al., aluminum phosphate being negatively charged and that vaccines containing aluminum phosphate as the adjuvant are known to stimulate IL-4 and $T_H2$-type of helper T cells as well as increasing levels of IgG1 and IgE antibodies (page 3, lines 17-24). Volkin et al., teach manipulating the adjuvants to possess a negative surface charge which will substantially retard DNA binding as being generated by any number of procedures which are well known and readily available (page 11-12, lines 24-2).

Therefore it would have been obvious to modify the immunogenic composition suitable for administration to a vertebrate host which comprises a protein antigen and a an adjuvant and a polynucleotide immunogenic component as taught by Dalemans et al., wherein the modification simply includes a mineral-based, negatively charged adjuvant as taught by Volkin et al., in order to advantageously provide an increased immune response and decrease nuclease digestion of the polynucleotide immunogenic component within the vertebrate host subsequent to immunization. One would have a reasonable expectation of success in combining the protein antigen + adjuvant and the polynucleotide immunogenic component since Dalemans and Volkin et al., teach vaccines/immunogenic compositions are well known to comprise negatively charged mineral-based adjuvants such as aluminum phosphate based adjuvants which carry a sufficiently negative charge in order to substantially retard binding to the polynucleotide component. Furthermore, all the claimed components, such as the protein antigen, the

mineral-based negatively charged adjuvant and polynucleotide components were well known and commercially available for use within the immunogenic composition and one skilled in the art could have combined the components as claimed by known methods with no change in their respective functions, wherein the combination would have yielded predictable and synergistic results including increasing the interleukin, T-cell, and antibodies results for one of ordinary skill in the art at the time of the invention.

***Conclusion***

5. No claims allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645